Specialty Conference

Participants

KENNETH LYONS JONES, MD
HECTOR E. JAMES, MD
JACK C. FISHER, MD

From the Department of Pediatrics, Divisions of Dysmorphology, Neurosurgery and Plastic Surgery, University of California Medical Center, San Diego.

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Craniosynostosis and Craniofacial Anomalies

KENNETH LYONS JONES, MD:* In most instances, craniosynostosis occurs as an isolated defect in otherwise completely normal children. However, sutural synostosis may represent only one abnormal feature in a multiple malformation syndrome. To provide appropriate prognosis and counseling on risk of recurrence, an accurate diagnosis must be made. Therefore, a practical approach to the evaluation of children with this condition is essential (Figure 1).

Classification of Craniosynostosis

When evaluating children with craniosynostosis, it is important first to make a distinction between primary craniosynostosis, which is due to an alteration in sutural growth, and secondary craniosynostosis, which is due to an impairment in the growth of the brain. In the latter situation the sutures fuse because they are not pushed apart by the brain's growth. The importance of making this distinction relates to prognosis. Children who have secondary craniosynostosis are, for the most part, severely impaired neurologically. They have a poor prognosis for intellectual development, and they do not benefit from surgical procedures that have been developed recently. Conversely, in most cases, children with primary craniosynostosis are normal neurologically, and their prognosis for intellectual development is very good. They are the best candidates for surgical operations because they have potentially normal brains which should grow properly following surgical correction.

Further classification of primary and secondary forms of craniosynostosis, as depicted in Figure 1, can be helpful in reaching a specific diagnosis, which is imperative for determining accurate prognosis and risk of recurrence. Primary craniosynostosis may represent a single primary defect in an otherwise normal child, or it may be one feature of a syndrome involving multiple malformations. Most cases involving a single primary defect are sporadic, representing isolated events in otherwise healthy families. Less frequently, primary craniosynostosis may be due to a single gene, in which instance the recurrence risk can be 0 percent, 25 percent or 50 percent, depending on whether it represents a fresh gene mutation, an autosomal recessive disorder or an autosomal dominant disorder in which one of the parents is similarly affected.

Primary craniosynostosis may also be seen as a feature of a multiple malformation syndrome. Table 1 lists multiple malformation syndromes known to be associated with craniosynostosis, a subject recently reviewed by Cohen.[1] Three of the disorders are due to abnormal chromosomes,[2-4] nine are disorders secondary to a single gene,[5-8] and one is secondary to a teratogen.[9] In addition, there are three multiple malformation syndromes for which causes remain unknown.[10-12] Of all of the disorders listed, the Crouzon syndrome (craniosynostosis, maxillary hypoplasia

*Assistant Professor of Pediatrics; Chief, Dysmorphology Service.
Reprint requests to: Hector E. James, MD, Division of Neurological Surgery H-893, University of California Medical Center, 225 West Dickinson Street, San Diego, CA 92103.

and shallow orbits) and the Apert syndrome (craniosynostosis, midfacial hypoplasia, and syndactyly) are the most common. Both of these conditions are genetically determined disorders with an autosomal dominant mode of inheritance.

Secondary craniosynostosis is sometimes the result of a single primary defect (that is, a child with a defect in brain development may be otherwise completely normal). Other times, the impairment of brain growth which occurs in craniosynostosis represents one feature in a multiple malformation syndrome. In most children in the former category, the cause of the defect and the risk of recurrence in other siblings are unknown. In some, an autosomal recessive mode of inheritance has been implicated; and in these instances the recurrent risk would be 25 percent. In a multiple malformation syndrome, the cause may be chromosomal, genetic or teratogenic. (The primary teratogenic cause is an intrauterine viral infection.)

Several clinical clues may be used to help distinguish between craniosynostosis due to decreased growth of the brain, and craniosynostosis due to a defect in sutural development:

- Children with secondary craniosynostosis frequently have a head circumference which is disproportionately small for their length and weight.
- The rate of head growth is usually substantially decreased in secondary craniosynostosis.
- Children with secondary craniosynostosis

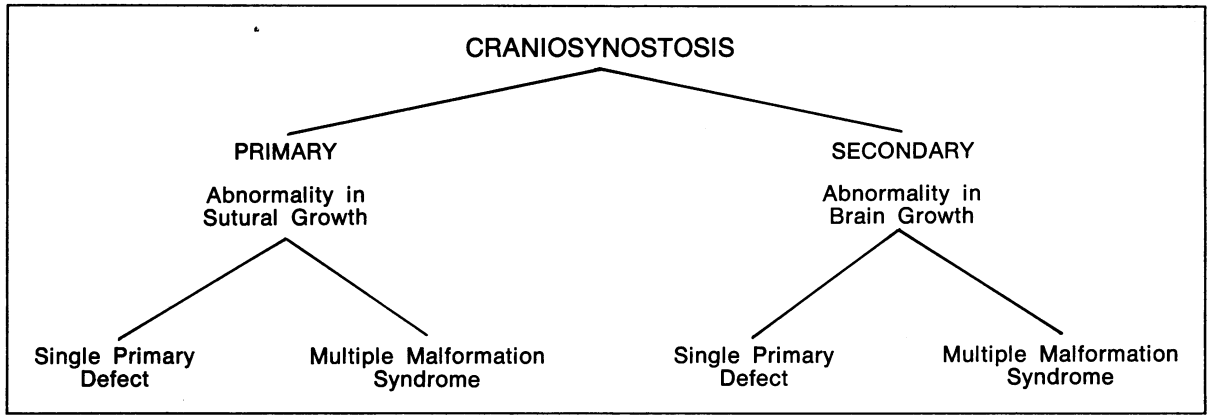

Figure 1.—Schematic classification of craniosynostosis.

TABLE 1.—*Syndromes With Craniosynostosis*

Syndrome	*Cause*
Chromosomal syndromes	
5p+ syndrome[2]	Trisomy for short arm of chromosome 5
7p− syndrome[3]	Deletion of short arm of chromosome 7
13q− syndrome[4]	Deletion of long arm of chromosome 13
Monogenic syndromes	
Apert syndrome[5]	Autosomal dominant
Crouzon syndrome[5]	Autosomal dominant
Pfeiffer syndrome[5]	Autosomal dominant
Saethre-Chotzen syndrome[5]	Autosomal dominant
Carpenter syndrome[5]	Autosomal dominant
Christian syndrome[6]	Autosomal recessive
Summitt syndrome[7]	Autosomal recessive
Baller-Gerold syndrome[5]	Autosomal recessive
Gorlin-Chaudhry-Moss syndrome[8]	Autosomal recessive
Teratogenically induced syndromes	
Aminopterin syndrome[9]	Aminopterin or methotrexate during pregnancy
Sporadic, incompletely delineated syndromes	
Herrmann-Opitz syndrome[10]	?
Herman-Pallister-Opitz syndrome[11]	?
Sakati-Nyhan-Tisdale syndrome[12]	?

have small, normally shaped heads, but because the brain is not growing, none of the sutures remain open. In primary craniosynostosis, on the other hand, the head is frequently asymmetric. The brain is growing at a normal rate but must adjust to the confined space. Thus, it continues to grow in areas where the sutures remain open but not where they have closed. This impairment in growth may lead to an abnormally shaped head.

• In most children with secondary craniosynostosis, neurological findings are abnormal. However, results of neurological examinations early in life usually are normal in children with primary craniosynostosis. In the rare cases of primary craniosynostosis in which all sutures are fused early in life, abnormal neurological findings will probably be noted. As the normal brain continues to grow in these children increased intracranial pressure will develop.

When carrying out a physical examination of a patient with craniosynostosis, it is important to be aware of an additional clinical clue. Structural defects of the limbs are the most common associated anomalies in multiple malformation syndromes associated with primary craniosynostosis. Each of the multiple malformation syndromes listed in Table 1 (except the Crouzon syndrome, the Christian syndrome and the Gorlin-Chaudhry-Moss syndrome) involves a defect in limb development, as well as craniosynostosis.

Reports of Cases

The presentation of a few brief case studies will illustrate the approach that has been outlined. The first case involved a child who was born after a normal 40-week gestation. Delivery was by cesarean section because of breech presentation. The mother noted that the infant had an extremely small head. When first seen by us at three months of age, the infant's head circumference was 34 cm (far below the third percentile). Results of the physical examination were otherwise normal, except for pronounced hypertonicity, irritability and developmental delay. Because of the disproportionately small, normocephalic head and abnormal neurological findings, our impression was that this child had secondary craniosynostosis. Furthermore, because all of the other results of her physical examination were completely normal, we felt that this represented a single primary defect in development. Further evaluation included a careful family history, transillumination of the head, a computerized axial tomographic (CAT) scan, and a study of blood specimens for viral titers. Transillumination showed multiple porencephalic cysts. A surgical

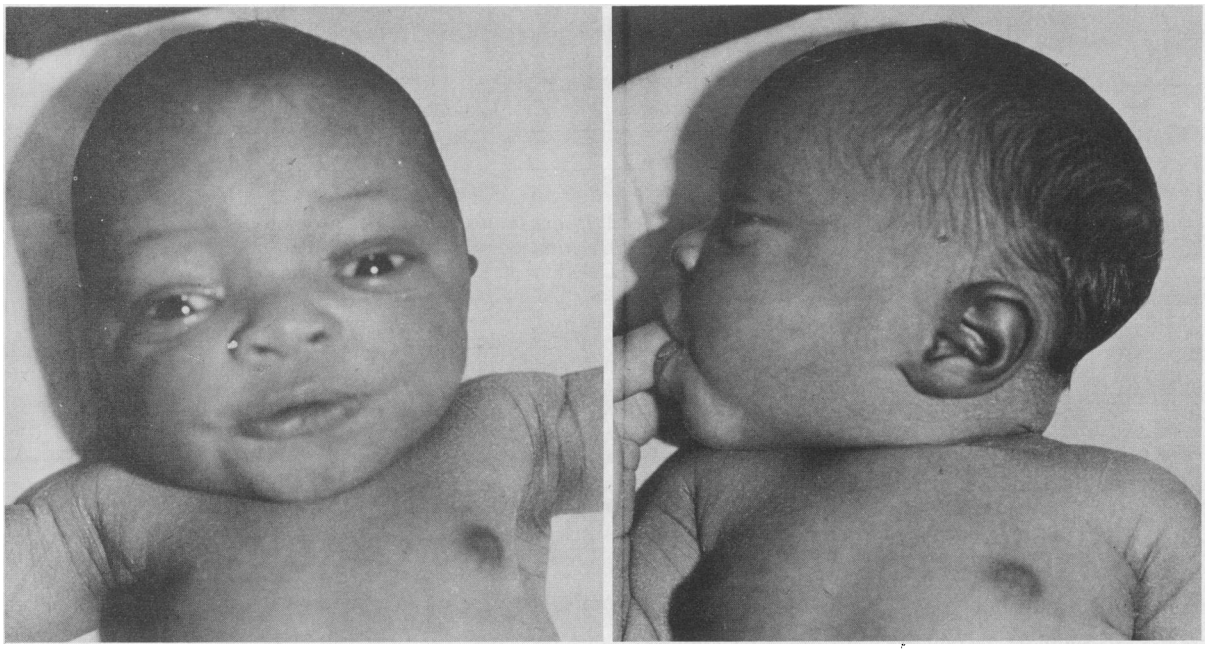

Figure 2.—Left, Frontal view—Newborn infant with asymmetry of the head secondary to synostosis of the sagittal and lambdoidal sutures. **Right,** Side view—Newborn infant with asymmetry of the head secondary to synostosis of the sagittal and lambdoidal sutures.

operation was not felt to be indicated because of the extent of disease in the brain.

The second case involved an infant who was born following a normal pregnancy and delivery. Birth weight and length as well as head circumference were normal. However, the newborn infant had pronounced asymmetry of the head (Figure 2). Results of a physical examination showed no other abnormalities. Based on the asymmetric shape of the infant's head and its normal circumference, and the unremarkable findings on neurological and physical examinations, it was felt that this patient had primary craniosynostosis that involved a single primary defect in an otherwise normal infant. Our evaluation was limited to studying roentgenograms of the skull which showed synostosis of the sagittal and lambdoidal sutures. The infant was referred for a neurosurgical operation.

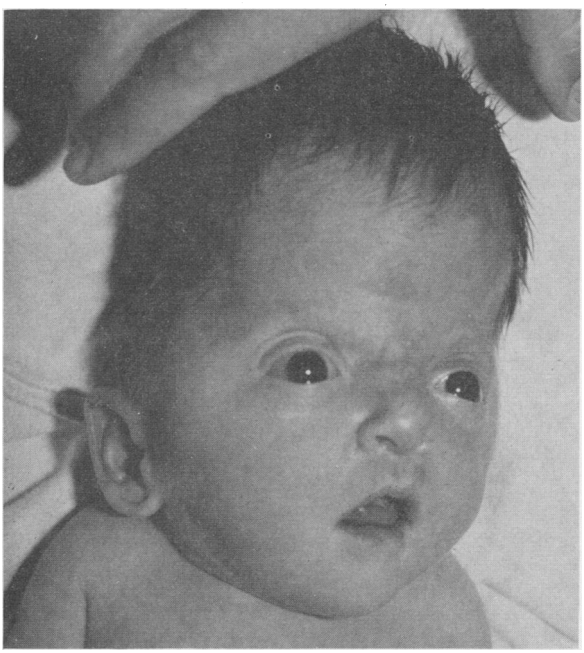

Figure 3.—Newborn infant with the Apert syndrome. Note the asymmetry of the calvarium, secondary to synostosis of the coronal and lambdoidal sutures.

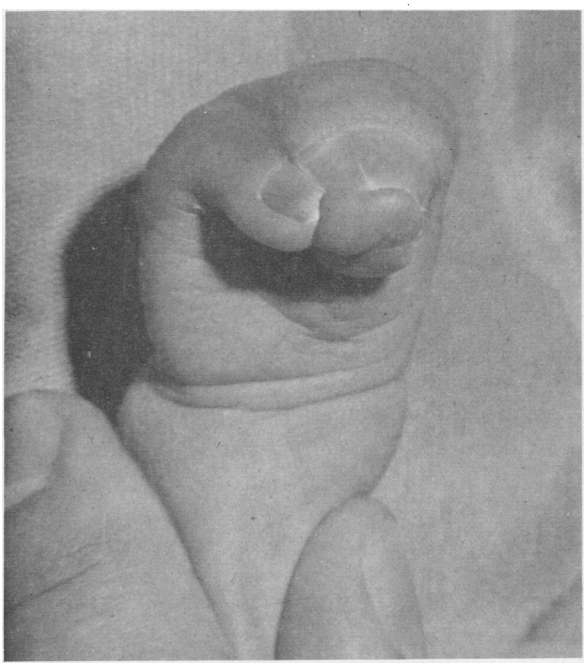

Figure 4.—The hand of the newborn infant with the Apert syndrome in Figure 3. Note the syndactyly of the fingers.

The third infant (Figure 3) was born after a 37-week, uncomplicated pregnancy and delivery. Birth weight was 2,860 grams (50th percentile), length at birth was 50 cm (75th percentile) and head circumference was 31 cm (10th percentile). There was considerable asymmetry of the craniofacial area. An examination disclosed ridges palpable over the lambdoidal and coronal sutures, hypoplastic supraorbital ridges, orbital hypertelorism, downslanting palpebral fissures and a cleft of the soft palate. In addition, there was bilateral soft-tissue syndactyly of fingers two through five, and of toes two through five as well (Figure 4). Results of the neurological examination showed no abnormalities. Because of the pronounced cranial asymmetry, the normal head circumference, and the unremarkable findings of the neurological examination, this infant was felt to have primary craniosynostosis as one feature of a multiple malformation syndrome. The features of this disorder are those of the Apert syndrome. Evaluation included roentgenograms of the skull, which showed synostosis of the lambdoidal and coronal sutures. A CAT scan was done to rule out a possible hydrocephalus. The infant was referred for a neurosurgical operation. Having made a diagnosis of the Apert syndrome, it was possible to give the family accurate counseling on the risk of recurrence. The Apert syndrome is an autosomal dominant disorder; both parents were normal, indicating that this child represented a fresh gene mutation. The risk of recurrence was 0 percent.

HECTOR E. JAMES, MD:* The most common form of primary synostosis is scaphocephaly, a condition in which the head growth cannot occur in

*Assistant Professor of Neurosurgery; Director, Pediatric Neurosurgery Service.

the transverse axis because of fusion of the sagittal suture. Instead, growth occurs primarily at the coronal, frontal, parietotemporal and lambdoidal sutures.[13] The next most common sutural involvement in primary synostosis is coronal synostosis; the unilateral form is more common than the bilateral form. In the bilateral form, the characteristic situation is a broad, high forehead. It has been observed that a combination of coronal and lambdoidal synostosis will produce oxycephaly or turricephaly (a tower-shaped head), because the only opening is the sagittal suture and the anterior fontanelle. Thus, it is clear that a thorough examination of a child with a significant calvarial abnormality is essential for diagnosing the syndrome and determining the location of the synostosis. Unfortunately, in children with partial syndromes, problems occur which frequently go unrecognized. In the past, these children would present with other disorders, such as later neurological handicaps, because of the impairment of brain growth.

Treatment of Synostosis

The primary objective of a surgical operation for synostosis is to allow adequate growth of the brain. The secondary objective is cosmetic. I want to emphasize the primary objective. The bulk of the brain's growth occurs by 12 months of age. When one looks at brain length, one sees that by one year of age it has already reached 80 percent of the full growth achieved in adulthood.[13,14] Therefore, if any problem occurs in the development of the calvarium, and it occurs within the first few months of life, as is often the case, the growth of the entrapped brain will be impaired. Under these conditions, signs and symptoms of increased intracranial pressure may develop, such as motor and developmental retardation or optic atrophy. Thus, although the brain can affect the development and molding of the calvarium of the cranial vault because of its tremendous force of expansion, early detection and prompt surgical treatment are extremely important for a positive end result.[14] It was recognized by some of the pioneers in the surgical treatment of this disorder that so-called simple synostosis or single-suture synostosis probably does not exist as an entity.[14]

Plain x-ray films represent a static way of looking at a pattern of sutural growth. We have tried to look at the synostosis more dynamically. A plain skull film may not be relevant because of motion artifact. We have had better results in looking at suture activity with isotope scanning, and this technique has provided us with insights into the disease process that we previously did not have. For instance, we have seen the lack of suture activity in some children because the suture is completely closed; in others the suture is inactive because of other underlying disease processes with which we are not entirely familiar.

We wish to present a classic case of scaphocephaly, to illustrate this approach. The plain x-ray films were not adequate. The diagnosis made was of lambdoidal synostosis, based on the presence of a very prominent ridge over the back of the head. However, there was an excessive anteroposterior length indicating scaphocephaly which could only be a consequence of sagittal closure. An isotope scan of the skull disclosed no coronal activity in this child at all. The posterior view showed an absence of activity in the lambdoidal suture line. The vertex view is the best one for observing the sagittal suture, and we could see a very hazy image, indicating that the suture was not turning over bone adequately. However, the most important feature of this patient's condition was not confirmed until during the surgical operation. Not only were the lambda and the sagittal sutures involved, but the coronal sutures were closed as well. Therefore, this child did not need the linear sagittal or lambdoidal craniectomy, but rather a more extensive surgical reconstructive procedure. We have discovered that this is the more common form of scaphocephaly, rather than the so-called simple or single-suture synostosis.

The first large series of patients were treated with surgical techniques instituted at the Boston Children's Medical Center,[13] and subsequent variants of these methods have been developed. As an example, one of the original techniques for avoiding the area of the sagittal sinus in treating scaphocephaly was the parasagittal craniectomy. After removing the bone on each side of the sagittal sinus, a synthetic material was interposed between the opening in the bone so as not tc allow growth between the two edges of bone. In this way, the transverse diameter of the skull was increased. This is the most unsatisfactory procedure from a cosmetic point of view. The patient came to the operating room with a long head and left the operating room with a long head. This type of procedure is also followed by a fairly high incidence of recurrence.[13,14] At present the pre-

ferred treatment for scaphocephaly, recognizing that there is more than just simple sagittal synostosis, is a multiple-suture synostectomy, with a total reconstruction of the calvarium. The incidence of recurrence is nil, and the cosmetic result is very good.[15]

JACK C. FISHER, MD:* Dr. Jones has outlined several syndromes in which deformities of the cranium and those of the face occur. Dr. James has provided an up-to-date summary of the current understanding regarding the origins of, and appropriate therapeutic response to, premature fusion of cranial sutures. Furthermore, he has hinted that the deformity we can see and feel may be a result of primary disturbances within the cranial base. I wish to discuss problems of the basal region further in order to explain the basis for our desire to avert facial deformity at the time of cranial synostectomy.

Nearly every new concept, by the time it achieves widespread acceptance, has for its origin a basic observation recorded well in advance of the time it could be fully understood or applied clinically. For example, we can look back to 1955 when Melvin Moss,[16] an orthodontist, summarized a series of rodent experiments in which a morphologic basis for the common cranial deformities that accompany synostosis could be defined. His cautious analysis of data derived from animal studies has not only survived the test of time, but also has proved applicable to humans. Moss proposed that ordinarily, cranial synostosis was secondary to another primary event. Malformations at the base of the skull preceded union of the cranial sutures. The fetal neural skull was considered to include a base, a neurocranial capsule, and a neural mass or primordial brain. Within the capsule, the dura and calvarial bones differentiated, the capsule retaining its attachment to the cranial base. Finally, according to Moss, the ultimate morphologic destiny of the cranium and facial mass appeared to be a derivative of brain growth on the one hand, and the restraining influence of the capsular attachments to the cranial base on the other. According to this hypothesis, dyscephaly in the form of cranial fusion becomes a manifestation or result of neurocranial malformation, rather than a primary cause. Thus, coronal synostosis can be considered the result of spatially malformed sphenoid wings, whereas sagittal synostosis is the result of a variation in dural attachments to the crista galli and cribriform plate. We have since learned of more subtle variations in cranial base sutures (the ethmofrontal and sphenofrontal sites of bony union) which, until recently, were beyond the site of gross radiologic inquiry, and certainly beyond the range of palpating fingers.

What does this mean to a specialist charged with the responsibility of preventing brain compression, or to a pediatrician who first perceives the presence of early sutural union? The answer is related in part to another frontier, largely technical, which has permitted correction of many of the major craniofacial malformations as well as stimulated a reexamination of their origin. The pioneering work of the French surgeon Paul Tessier[17] prompted a more courageous surgical approach to severe facial deformities. Tessier's original work was done almost exclusively on adolescents and early adults with fully developed deformities (such as craniofacial dysostosis, also called the Crouzon syndrome). His was a largely technological contribution, extending principles learned by plastic surgeons during the world wars while treating extensive maxillofacial injuries, and relying on simultaneous exposure of the anterior brain vault and facial skeleton.[17]

Soon the obvious questions were asked: why not intercept these deformities at an earlier age,[14] and can their full expression be prevented by early surgical intervention—that is, within a few weeks of birth? The answer to both questions was yes. Mohr, Hoffman and associates[14] have recorded the association between cranial and facial malformations presumed to originate from the cranial base. They have also led the movement to correct the origins of the facial components of these deformities well in advance of their full expression. One example is the identification of the periorbital components of unicoronal and bicoronal synostosis, with associated retrusion of the brow(s) and shallowness of the orbit(s). It can be presumed that if left alone, these orbital synostoses will ultimately lead to craniofacial dysmorphism of the Apert or Crouzon variety. Experience with surgical advance of the restrained orbital rims suggests that permanent deformity may be averted, particularly when orbital repositioning can be carried out very soon after birth.

Conclusion

The lessons, some old and some new, can be listed as follows: (1) Primary craniosynostosis

*Associate Professor of Surgery; Head, Plastic Surgery Division.

may never be a primary event, but rather a result of abnormal development at the cranial base. (2) Malformations of the cranium are often associated with malformations of facial development. (3) Clinicians faced with a child with craniosynostosis are also presented with an urgent need to prevent brain entrapment, as well as an opportunity to halt progression of the facial deformity. (4) Finally, proper management of this array of developmental disorders requires close communication between several specialists, including a pediatric dysmorphologist, a neurosurgeon and a plastic surgeon.

REFERENCES

1. Cohen MM Jr: Genetic perspectives on craniosynostosis and syndromes with craniosynostosis. J Neurosurg 47:886-898, 1977

2. Opitz JM, Patau K: A partial trisomy 5p— syndrome. Birth Defects 11:191-200, 1975

3. McPherson E, Hall JG, Hickman R: Short arm deletion and craniosynostosis—A 7p— syndrome. Hum Genet 35:117-123, 1976

4. Orbeli DJ, Lurie IW, Gorosheuko JL: The syndrome associated with the partial D-monosomy—Case report and review. Humangenetik 13:296-308, 1971

5. Cohen MM Jr: An etiologic and nosologic overview of craniosynostosis syndromes. Birth Defects 11:137-189, 1975

6. Christian JC, Andrews PA, Conneally PM, et al: The adducted thumbs syndrome—An autosomal recessive disease with arthrogryposis dysmyelination, craniostenosis and cleft palate. Clin Genet 2:92-103, 1971

7. Summitt RL: Recessive acrocephalosyndactlyly with normal intelligence. Birth Defects 5:35-38, 1969

8. Gorlin RJ, Chaudhry AP, Moss ML: Craniofacial dysostosis, patent ductus arteriosus, hypertrichosis, hypoplasia of labia majora, dental and eye anomalies. J Pediatr 56:778-785, 1960

9. Shaw EB, Steinbach HL: Aminopterin-induced fetal malformation—Survival of an infant after attempted abortion. Am J Dis Child 115:477-482, 1968

10. Herrmann J, Opitz JM: An unusual form of acrocephalosyndactyly. Birth Defects 5:39-42, 1969

11. Herrmann J, Pallister PD, Opitz JM: Craniosynostosis and craniosynostosis syndromes. Rocky Mtn Med J 66:45-56, May 1969

12. Sakati N, Nyhan WL, Tisdale WK: A new syndrome with acrocephalopolysyndactyly, cardiac disease and distinctive defects of the ear skin and lower limbs. J Pediatr 79:104-109, 1971

13. Matson DD: Neurosurgery of Infancy and Childhood, 2nd Ed. Springfield, IL, Charles C Thomas, 1969

14. Mohr G, Hoffman HJ, Munro IR et al: Surgical management of unilateral and bilateral coronal craniosynostosis: 21 years of experience. Neurosurgery 2:83-92, 1978

15. Stein CS, Schut L: Management of scaphocephaly. Surg Neurol 7:153-155, 1977

16. Moss ML, Greenberg SN: Postnatal growth of the human skull base. Angle Orthod 25:77-84, 1955

17. Tessier P: Relationship of craniostenosis to craniofacial dysostoses and to faciostenosis. Plastic Reconstr Surg 48:224-237, 1971

Relationship of Caffeine to Fibrocystic Disease

JOHN P. MINTON at Ohio State University in Columbus has worked for a number of years studying the effects of adenosine monophosphate levels in breast tissue. As an offshoot of that, he became interested in . . . substances called methylxanthenes. Caffeine—such as in coffee, tea, colas and cocoa—belongs to the methylxanthene group. These seem to inactivate a hormone which should stop the action of drugs that stimulate activity within the cell to produce fibrous tissue and cyst fluid. On the presumption that the consumption of methylxanthene in the form of caffeine is a cause of fibrocystic disease, Minton and his group eliminated caffeine from the diet of women with symptomatic lumpy fibrocystic disease. . . . Of 20 patients who were having ongoing and continuing symptomatic troubles, 13 had complete resolution of the process. . . . Of a group of 27 who continued to consume coffee, tea, colas, and so forth, only one had a corresponding regression. The long-term follow-up studies have continued to confirm the results. . . . There is a strong suggestion that caffeine, as one of the methylxanthene group, may well have something to do with the perpetuation of and increase of symptoms of fibrocystic disease.

—ELMER K. SANDERS, MD, *Houston*

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